

REMARKS/ARGUMENTS

Applicants respectfully request reconsideration of this application in light of the amendments and arguments presented herein.

By the amendments, Applicants do not acquiesce to the propriety of any of the Office's rejections and do not disclaim any subject matter to which Applicants are entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 U.S.P.Q.2d 1865 (U.S. 1997).

In the Claims

Claims 1, 3-5, 7, 8, 10-12, 14, 16-18, 20 and 21 are pending in this application.

The listing of claim 1 herein reflects the amendment made in the previous response (filed January 21, 2009) that was not properly introduced.

Claim 1 has been amended to replace the term "a drug" in the preamble with the term "said antihistamine".

Claim 12 has been amended to correct a typographical error.

No new matter has been introduced as a result of the claim amendments.

Information Disclosure Statement

The Office asserts that the Information Disclosure Statement submitted January 21, 2009 fails to comply with 37 CFR §1.98(a)(1). Applicants respectfully assert that the reference (Respiratory Drug Delivery VIII, 2002) was published after the filing date of the instant application and is not prior art. This reference was provided solely in support of statements made by Applicants in the response filed January 21, 2009. Therefore, Applicants believe that a formal Information Disclosure Statement under 37 CFR §1.98(a)(1) is not required with regard to this reference.

35 U.S.C. §112 Rejections

Claims 1 and 2 have been rejected under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office asserts that the limitation "suitable

for administration of a drug” renders the claim confusing. Applicants have amended claim 1 to replace the term “drug” with “antihistamine”.

Claim 2 had been previously cancelled. Therefore, Applicants are unsure of which claim the Office is referring to and have not been able to address this part of the rejection.

Therefore, in light of the amendments to claim 1, Applicants respectfully request withdrawal of the rejection on this basis.

35 U.S.C. §103 Rejections

Claims 1, 3-5, 7, 8, 10-12, 14, 16-18, 20 and 21 have been rejected under 35 USC §103(a) as allegedly being unpatentable over Steiner et al. (US Pat. 5,503,852) in view of Illum (US Pat. 5,690,954).

Applicants respectfully traverse.

To maintain a proper rejection under 35 U.S.C. §103, the Office must meet four conditions to establish a *prima facie* case of obviousness. First, the Office must show that the prior art suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. Second, the Office must show that the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in an applicant's disclosure. Third, the prior art must teach or suggest all the claim limitations. *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Fourth, if an obviousness rejection is based on some combination of prior art references, the Office must show a suggestion, teaching, or motivation to combine the prior art references (“the TSM test”). *In re Dembiczak*, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). Following *KSR Int'l Co. v. Teleflex, Inc.*, this fourth prong of the *prima facie* obviousness analysis must not be applied in a rigid or formulaic way such that it becomes inconsistent with the more flexible approach of *Graham v. John Deere*, 383 U.S. 1, 17-18 (1966); 127 S. Ct. 1727 (2007). It must still be applied, however, as the TSM test captures the important insight

that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.* at 1741 (citing *United States v. Adams*, 383 U.S. 39, 50-52 (1966)).

The instant claims are drawn to compositions, devices and methods for nasal administration of antihistamines in a dry powder comprising microparticles comprising the antihistamine and a diketopiperazine wherein the microparticles are sized such that the particles are preferentially retained in the nasal cavity and have a particle size of between about 10 microns and about 20 microns in diameter and wherein more than 50% of the microparticles have a particle size greater than about 10 microns, and wherein the composition does not pass into the pulmonary system.

Steiner discloses particles between 0.1 to 10 microns in diameter. Steiner does not disclose microparticles wherein more than 50% of the microparticles have a particle size greater than about 10 microns. The microparticles of Steiner are primarily used for delivery to the pulmonary system, a use requiring smaller particles. In paragraph [0008] of the instant publication, Applicants state "[a] critical aspect is the size range of the microparticles, between approximately 10 and 20 microns in diameter, which causes the particles to be retained in the nasal region, and not passed into the pulmonary system or mouth." Therefore, Steiner does not teach or suggest microparticles wherein the majority of the particles are greater than 10 microns in size and furthermore, Steiner does not suggest particles which are retained in the nasal cavity, rather than passing into the lungs.

The Office asserts on page 6, lines 3-4 of the Office Action mailed April 8, 2009 (hereinafter "OA"), page 7 that "[a]bsent a showing of evidence to the contrary, Steiner's microparticles would be suitable for nasal administration."

Applicants hereby submit a declaration under 37 CFR §1.132 by Dr. Marshall Grant, Senior Director in the Research & Development Group at MannKind Corporation, the assignee of the present application. This declaration was previously filed in related co-pending application 11/843,863 (which is a continuation of the instant application). Dr. Grant asserts that the microparticles for nasal administration of the instant invention

are physically different from the microparticles taught by Steiner. Furthermore Steiner does not teach or suggest a method for making microparticles for nasal delivery or microparticles that are useful for nasal delivery.

The microparticles of Steiner are prepared by a process of co-precipitation in which the diketopiperazine is dissolved in a solution and then the solution is mixed with a second solution containing the active agent. The microparticles are then precipitated by the addition of acid or base (Steiner column 9, line 55 through column 10, line 8). The resultant microparticles have the active agent encapsulated within the diketopiperazine microparticle during the co-precipitation process.

In contrast, the microparticles of the instant invention are formed by obtaining pre-formed microparticles of diketopiperazine of a controlled size (10-20 microns) and mixing the pre-formed microparticles with an antihistamine such that the antihistamine is coated on the surface of the diketopiperazine microparticles (see Example 5 of the instant specification). As asserted by Dr. Grant, the coated microparticles of the instant claims (termed "complexed" by Dr. Grant) and the co-precipitated microparticles of Steiner have different physical and physicochemical characteristics (see Grant declaration, paragraphs 11-18).

Furthermore, the Applicants own publication (Wilson et al. Respiratory Drug Delivery VIII, 2002), submitted as Exhibit 2 of the Grant Declaration and published after the priority date of the instant application, states that particles prepared for inhalation have typical physical and aerodynamic characteristics that direct them to the deep lung. Particles for delivery to the deep lung have mass mean aerodynamic diameter of 2-4 microns. The authors go on to state that the goal of the published study (the subject of the instant application) was to produce larger particles for nasal inhalation (at least 10 microns in diameter) to reduce drug carry-over to the taste centers and more precisely target the nasal mucosa. (See Wilson page 545, Introduction). Therefore, the Wilson reference establishes the 10 micron critical lower limit of microparticle size for optimal nasal administration without deposition of the microparticles in the taste centers or in the deep lung. The Wilson reference is provided solely for support of the Applicant's

statements in the response filed January 21, 2009 and in the Grant Declaration. The Wilson reference is not prior art as it was published after the priority date of the instant application. Therefore, Applicants believe it is not necessary to file the Wilson reference in an Information Disclosure Statement.

Moreover, Applicants respectfully assert that the instant specification supports Applicants' assertions that compositions comprising microparticles in which at least 50% of the microparticles have a size greater than 10 microns are retained in the nasal cavity and do not pass into the pulmonary system. Example 3 of the instant application describes a study which compares particles administered as a dry powder wherein the particles have a mean particle size of 20 microns and wherein more than 50% of the particles have a size greater than 10 microns (the particles of Formulation 1 and Formulation 2). When administered to subjects, along with a commercial liquid nasal spray as control, the dry powder formulations did not impart a bitter taste to the subjects while the liquid nasal spray imparted a bitter taste. The presence of a bitter taste is indicative of the liquid nasal spray passing into the mouth and pulmonary system and not being retained in the nasal cavity. Furthermore, the particles having a mean particle size of 20 microns and wherein more than 50% of the particles have a size greater than 10 microns were efficacious in relieving rhinorrhea and sneezing, indicating that they were retained in the nasal cavity. Therefore, the claimed microparticles are retained in the nasal cavity and do not pass into the pulmonary system.

The Applicants also assert that Steiner teaches away from the instantly claimed invention. In *KSR*, the Court held "When the prior art teaches away from combining certain known elements, discovery of successful means of combining them is more likely to be nonobvious." (*KSR*, USPQ2d at 1395).

Applicants respectfully assert that Steiner teaches away from using larger microparticles because a composition in which 50% or more of the microparticles are between about 10 microns and about 20 microns in size will deliver the particles to the nasal cavity and these larger particles will not reach the lungs, the target of Steiner's composition. As stated in Wilson et al. (see Introduction), for delivery to the deep lung,

the diameter of the particles is preferably 2-4 microns. Therefore, contrary to the statement on page 11 of the OA, the particles of Steiner are not suitable for administration to, and retention in, the nasal cavity without passing into the pulmonary system.

Illum does not remedy the deficiencies of Steiner. Illum teaches drug delivery systems comprising microsphere particles containing an active drug and a bioavailability enhancer. Illum does disclose antihistamines as a long list of drugs (column 8, line 59 through column 9, line 52). Illum states that the microspheres should be of a size between 10 and 100 microns (column 6, lines 13-14). In column 6, line 28 through column 7, line 54, Illum presents examples of microspheres and their sizes. Starch microspheres were prepared having a mean size of 33 microns (column 6, lines 52-53); albumin microspheres were prepared having a size range of 40-60 microns (column 7, lines 1-2) and a mean size of 43 ± 6 microns (column 7, lines 19-20); gelatin microspheres were prepared having a mean particle size of 70 microns (column 7, lines 30-31) and 60 microns (column 7, lines 41-42); and chitosan microspheres were prepared having a size range of 10-90 microns (column 7, lines 53-54). While Illum teaches microspheres made from a variety of materials, none of the materials produced microparticles in which the majority of the microparticles are in the range of 10-20 microns. In fact, the majority of the microspheres produced by Illum are greater than 20 microns in size, teaching away from the instant claims which recite microparticles of 10-20 micron size as optimal for effective delivery of drugs to the nasal mucosa.

While there is overlap in the range of the claimed microparticles and the microspheres of Illum, Illum does not teach or suggest microparticles between about 10 microns and about 20 microns in diameter wherein more than 50% of the microparticles have a particle size greater than about 10 microns.

Furthermore, there is not suggestion in the teachings of Steiner and Illum to take the particles of Steiner, notwithstanding that they are not sized for administration to and retention in the nasal cavity, with the antihistamines disclosed in a "laundry list" of drugs disclosed by Illum to yield the presently claimed invention.

Accordingly, the teaching of Steiner in combination with Illum fails to teach or suggest all elements of the claimed invention and there is not suggestion to combine the references. Therefore, claims 1, 3-5, 7, 8, 10-12, 14, 16-18, 20 and 21 are not obvious under 35 U.S.C. §103(a) over Steiner in view of Illum and Applicants respectfully request that this rejection be withdrawn.

REMARKS/ARGUMENTS

In light of the foregoing, Applicants respectfully assert that the pending claims are in condition for allowance and request that a timely Notice of Allowance be issued in this case.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 50-3207.

Respectfully submitted,

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